



## EXHIBIT C

Claims Pending After Entry of the Preliminary Amendment Dated August 20, 2001

U.S. Patent Application Serial No. 09/783,487

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1. A collection of lines of transgenic animals comprising two or more of said lines of transgenic animals wherein each of said transgenic animals comprises a transgene, said transgene comprising (a) first sequences coding for a selectable or detectable marker protein; and (b) regulatory sequences of a characterizing gene corresponding to an endogenous gene or ortholog of an endogenous gene operably linked to said first sequences such that said first sequences are expressed in said transgenic animal with an expression pattern that is substantially the same as the expression pattern of said endogenous gene in a non-transgenic animal or anatomical region thereof, wherein the characterizing gene is different for each of said transgenic animals, and wherein said transgene is present in the genome at a site other than where the endogenous gene is located.

2. The collection of lines of transgenic animals of claim 1 wherein said transgenic animals are transgenic mice.

3. The collection of lines of transgenic animals of claim 1 which comprises ten or more lines of transgenic animals.

4. The collection of lines of transgenic animals of claim 1 which comprises fifty or more lines of transgenic animals.

5. The collection of lines of transgenic animals of claim 1 wherein said transgene further comprises a coding sequence of said characterizing gene.

6. The collection of lines of transgenic animals of claim 5 wherein said first sequences are inserted or replace sequences 5' of said coding sequence of said characterizing gene.

7. The collection of lines of transgenic animals of claim 1 wherein said first sequences are operably linked to an IRES sequence that is not operably linked to a coding sequence of said characterizing gene.

8. The collection of lines of transgenic animals of claim 5 wherein said first sequences are fused in frame to the ATG start codon of said coding sequence of said characterizing gene.

9. The collection of lines of transgenic animals of claim 1 wherein said characterizing gene is not functionally expressed from said transgene.

10. The collection of lines of transgenic animals of claim 1 wherein said first sequences encode a detectable enzyme.

11. The collection of lines of transgenic animals of claim 10 wherein said detectable enzyme is  $\beta$ -lactamase.

12. The collection of lines of transgenic animals of claim 1 wherein said first sequences encode a fluorescent protein.

13. The collection of lines of transgenic animals of claim 12 wherein fluorescent protein is a green fluorescent protein (GFP).

14. The collection of lines of transgenic animals of claim 1 wherein each said endogenous gene is expressed in the same tissue.

15. The collection of lines of transgenic animals of claim 1 wherein each said endogenous gene is specifically expressed in a subset of neurons.

16. The collection of lines of transgenic animals of claim 1 wherein each said endogenous gene is endogenously expressed in neuronal cells.

17. The collection of lines of transgenic animals of claim 1 wherein each of said endogenous genes endogenously expresses a protein product that is a part of an adrenergic or noradrenergic neurotransmitter pathway, a cholinergic neurotransmitter pathway, a dopaminergic neurotransmitter pathway, a GABAergic neurotransmitter pathway, a glutaminergic neurotransmitter pathway, a glycinergic neurotransmitter pathway, a histaminergic neurotransmitter pathway, a neuropeptidergic neurotransmitter pathway, a serotonergic neurotransmitter pathway, or the sonic hedgehog signaling pathway, is a nucleotide receptor, an ion channel, a marker of undifferentiated or not fully differentiated nerve cells, a calcium binding protein, or a neurotrophic factor receptor.

18. The collection of lines of transgenic animals of claim 1 wherein all of said endogenous genes are functionally related.

19. The collection of lines of transgenic animals of claim 1 wherein each of said endogenous genes is implicated in the same physiological or disease state.

20. The collection of lines of transgenic animals of claim 19 wherein the physiological or disease state is a neurological or psychiatric disease.

21. The collection of lines of transgenic animals of claim 20 wherein the neurological or psychiatric disease is schizophrenia, schizotypal personality disorder, psychosis, a schizoaffective disorder manic type disorder, a bipolar affective disorder, a bipolar affective (mood) disorder with hypomania and major depression (BP-II), a unipolar affective disorder, unipolar major depressive disorder, dysthymic disorder, a obsessive-compulsive disorder, a phobia, a panic disorder, a generalized anxiety disorder, a somatization disorder, hypochondriasis, or an attention deficit disorder.

22. The collection of lines of transgenic animals of claim 1 wherein each of said endogenous genes is implicated in the same physiological or behavioral response.

23. The collection of lines of transgenic animals of claim 22 wherein said physiological or behavioral response is pain, sleeping, feeding, fasting, sexual behavior or aggression.

24. The collection of lines of transgenic animals of claim 1 wherein each of said endogenous genes is expressed in neuronal cells involved in regulation of feeding behavior.

25. The collection of lines of transgenic animals of claim 1 wherein each of said endogenous genes is expressed in a different tissue.

26. The collection of lines of transgenic animals of claim 1 wherein each of said endogenous genes is implicated in a different physiological or disease state.

27. The collection of lines of transgenic animals of claim 1 wherein each of said endogenous genes is implicated in a different physiological or behavioral response.

28. A collection of lines of transgenic animals comprising two or more of said lines of transgenic animals wherein each of said transgenic animals comprises a transgene, said transgene comprising (a) first sequences coding for an activator or repressor of expression of second sequences encoding a detectable or selectable marker; and (b) regulatory sequences of a characterizing gene corresponding to an endogenous gene or ortholog of an endogenous gene operably linked to said first sequences such that said first sequences are expressed in said transgenic animal with an expression pattern that is substantially the same as the expression pattern of said endogenous gene in a non-transgenic animal or anatomical region thereof, wherein the characterizing gene is different for each of said transgenic animals, and wherein said transgene is present in the genome at a site other than where the endogenous gene is located; each of said transgenic animals also comprising said second sequences operably linked to an expression control element activatable or repressible by said activator or repressor.

29. The collection of lines of transgenic animals of claim 28 wherein said second sequences are contained within said transgene.

30. The collection of lines of transgenic animals of claim 28 wherein said second sequences are not contained within said transgene.

31. The collection of lines of transgenic animals of claim 30 wherein said second sequences are introduced into the genome of said transgenic animal by breeding.

32. A method of making a collection of lines of transgenic animals said method comprising

- (a) introducing into the genome of a founder animal a transgene comprising (i) first sequences coding for a selectable or detectable marker protein and (ii) regulatory sequences of a characterizing gene corresponding to an endogenous gene or ortholog of an endogenous gene operably linked to said first sequences such that said first sequences are expressed in said transgenic animal with an expression pattern that is substantially the same as the expression pattern of said endogenous gene in a non-transgenic animal or anatomical region thereof;
- (b) breeding said founder animal to produce a line of transgenic animals; and
- (c) repeating steps (a) and (b) one or more times, each time with a different characterizing gene to generate one or more additional lines of transgenic animals,

thereby generating said collection of lines of transgenic animals.

33. The method of claim 32 wherein said transgenic animals are transgenic mice.

34. The method of claim 32 wherein said collection comprises ten or more lines of transgenic animals.

35. The method of claim 32 wherein said collection comprises fifty or more lines of transgenic animals.

36. The method of claim 32 wherein said transgene further comprises a coding sequence of said characterizing gene.

37. The method of claim 36 wherein said first sequences are inserted or replace sequences 5' of said coding sequence of said characterizing gene.

38. The method of claim 32 wherein said first sequences are operably linked to an IRES sequence that is not operably linked to a coding sequence of said characterizing gene.

39. The method of claim 36 wherein said first sequences are fused in frame to the ATG start codon of said coding sequence of said characterizing gene.

40. The method of claim 32 wherein said characterizing gene is not functionally expressed from said transgene.

41. The method of claim 32 wherein said first sequences encode a detectable enzyme.

42. The method of claim 41 wherein said detectable enzyme is  $\beta$ -lactamase.

43. The method of claim 32 wherein said first sequences encode a fluorescent protein.

44. The method of claim 43 wherein fluorescent protein is a GFP.

45. The method of claim 32 wherein each said endogenous gene is expressed in the same tissue.

46. The method of claim 32 wherein each said endogenous gene is specifically expressed in a subset of neurons.

47. The method of claim 32 wherein each said endogenous gene is endogenously expressed in neuronal cells.

48. The method of claim 32 wherein each of said endogenous genes endogenously expresses a protein product that is a part of an adrenergic or noradrenergic neurotransmitter pathway, a cholinergic neurotransmitter pathway, a dopaminergic neurotransmitter pathway, a GABAergic neurotransmitter pathway, a glutaminergic neurotransmitter pathway, a glycinergic neurotransmitter pathway, a histaminergic neurotransmitter pathway, a neuropeptidergic neurotransmitter pathway, a serotonergic neurotransmitter pathway, or the sonic hedgehog signaling pathway, is a nucleotide receptor, an ion channel, a marker of undifferentiated or not fully differentiated nerve cells, a calcium binding protein, or a neurotrophic factor receptor.

49. The method of claim 32 wherein all of said endogenous genes are functionally related.

50. The method of claim 32 wherein each of said endogenous genes is implicated in the same physiological or disease state.

51. The method of claim 50 wherein the physiological or disease state is a neurological or psychiatric disease.

52. The method of claim 51 wherein the neurological or psychiatric disease is schizophrenia, schizotypal personality disorder, psychosis, a schizoaffective disorder manic type disorder, a bipolar affective disorder, a bipolar affective (mood) disorder with hypomania and major depression (BP-II), a unipolar affective disorder, unipolar major depressive disorder, dysthymic disorder, a obsessive-compulsive disorder, a phobia, a panic disorder, a generalized anxiety disorder, a somatization disorder, hypochondriasis, or an attention deficit disorder.

53. The method of claim 32 wherein each of said endogenous genes is implicated in the same physiological or behavioral response.

54. The method of claim 53 wherein said physiological or behavioral response is pain, sleeping, feeding, fasting, sexual behavior or aggression.

55. The method of claim 32 wherein each of said endogenous genes is expressed in neuronal cells involved in regulation of feeding behavior.

56. The method of claim 32 wherein each of said endogenous genes is expressed in a different tissue.

57. The method of claim 32 wherein each of said endogenous genes is implicated in a different physiological or disease state.

58. The method of claim 32 wherein each of said endogenous genes is implicated in a different physiological or behavioral response.

59. The method of claim 32 wherein prior to introduction into said founder animal said transgene is contained within a bacterial artificial chromosome (BAC).

60. The method of claim 32 wherein said transgene is introduced by pronuclear injection.

61. A method of making a collection of lines of transgenic animals, said method comprising

- (a) introducing into the genome of a founder animal a transgene comprising (i) first sequences coding for an activator or repressor of expression of second sequences encoding a detectable or selectable marker and (ii) regulatory sequences of a characterizing gene corresponding to an endogenous gene or ortholog of an endogenous gene operably linked to said first sequences such that said first sequences are expressed in said transgenic animal with an expression pattern that is substantially the same as the expression pattern of said endogenous gene in a non-transgenic animal or anatomical region thereof;
- (b) breeding said founder animal to produce a line of transgenic animals; and

- (c) repeating steps (a) and (b) one or more times, each time with a different characterizing gene to generate one or more additional lines of transgenic animals,

thereby generating said collection of lines of transgenic animal, wherein each of said transgenic animals also comprises said second sequences operably linked to an expression control element activatable or repressible by said activator or repressor.

62. The method of claim 61 wherein said second sequences are contained within said transgene.

63. The method of claim 61 wherein said second sequences are not contained within said transgene.

64. The method of claim 63 wherein said second sequences are introduced into the genome of said transgenic animal by breeding.

65. A collection of vectors for making transgenic animals, said collection comprising two or more of said vectors wherein each of said vectors comprises a transgene, said transgene comprising (a) first sequences coding for a selectable or detectable marker protein and (b) regulatory sequences of a characterizing gene corresponding to an endogenous gene or ortholog of an endogenous gene operably linked to said first sequences such that when said transgene is present in the genome of a transgenic animal said first sequences are expressed in said transgenic animal with an expression pattern that is substantially the same as the expression pattern of said endogenous gene in a non-transgenic animal or anatomical region thereof, wherein the characterizing gene is different for each of said vectors.

66. The collection of vectors of claim 65 which comprises ten or more vectors.

67. The collection of vectors of claim 65 which comprises fifty or more vectors.

68. The collection of vectors of claim 65 wherein said transgene further comprises a coding sequence of said characterizing gene.

69. The collection of vectors of claim 68 wherein said first sequences are inserted or replaces sequences 5' of said coding sequence of said characterizing gene.

70. The collection of vectors of claim 65 wherein said first sequences are operably linked to an IRES sequence that is not operably linked to a coding sequence of said characterizing gene.

71. The collection of vectors of claim 68 wherein said first sequences are fused in frame to the ATG start codon of said coding sequence of said characterizing gene.

72. The collection of vectors of claim 65 wherein said characterizing gene is not functionally expressed from said transgene.

73. The collection of vectors of claim 65 wherein said first sequences encode a detectable enzyme.

74. The collection of vectors of claim 73 wherein said detectable enzyme is  $\beta$ -lactamase.

75. The collection of vectors of claim 65 wherein said first sequences encode a fluorescent protein.

76. The collection of vectors of claim 75 wherein fluorescent protein is a GFP.

77. The collection of vectors of claim 65 wherein each said endogenous gene is specifically expressed in a subset of neurons.

78. The collection of vectors of claim 65 wherein each said endogenous gene is expressed in the same tissue.

79. The collection of vectors of claim 65 wherein each said endogenous gene is endogenously expressed in neuronal cells.

80. The collection of vectors of claim 65 wherein each of said endogenous genes endogenously expresses a protein product that is a part of an adrenergic or noradrenergic neurotransmitter pathway, a cholinergic neurotransmitter pathway, a dopaminergic neurotransmitter pathway, a GABAergic neurotransmitter pathway, a glutaminergic neurotransmitter pathway, a glycinergic neurotransmitter pathway, a histaminergic neurotransmitter pathway, a neuropeptidergic neurotransmitter pathway, a serotonergic neurotransmitter pathway, or the sonic hedgehog signaling pathway, is a nucleotide receptor, an ion channel, a marker of undifferentiated or not fully differentiated nerve cells, a calcium binding protein, or a neurotrophic factor receptor.

81. The collection of vectors of claim 65 wherein all of said endogenous genes are functionally related.

82. The collection of vectors of claim 65 wherein each of said endogenous genes is implicated in the same physiological or disease state.

83. The collection of vectors of claim 82 wherein the physiological or disease state is a neurological or psychiatric disease.

84. The collection of vectors of claim 83 wherein the neurological or psychiatric disease is schizophrenia, schizotypal personality disorder, psychosis, a schizoaffective disorder manic type disorder, a bipolar affective disorder, a bipolar affective (mood) disorder with hypomania and major depression (BP-II), a unipolar affective disorder, unipolar major depressive disorder, dysthymic disorder, a obsessive-compulsive disorder, a phobia, a panic disorder, a generalized anxiety disorder, a somatization disorder, hypochondriasis, or an attention deficit disorder.

85. The collection of vectors of claim 65 wherein each of said endogenous genes is a member of a group of genes that are implicated in the same physiological or behavioral response.

86. The collection of vectors of claim 85 wherein said physiological or behavioral response is pain, sleeping, feeding, fasting, sexual behavior or aggression.

87. The collection of vectors of claim 65 wherein each of said endogenous genes is expressed in neuronal cells involved in regulation of feeding behavior.

88. The collection of vectors of claim 65 wherein each of said endogenous genes is expressed in a different tissue.

89. The collection of vectors of claim 65 wherein each of said endogenous genes is implicated in a different physiological or disease state.

90. The collection of vectors of claim 65 wherein each of said endogenous genes is implicated in a different physiological or behavioral response.

91. The collection of vectors of claim 65 wherein said vectors are BACs.

92. A collection of vectors for making transgenic animals, said collection comprising two or more of said vectors wherein each of said vectors comprises a transgene, said transgene comprising (a) first sequences coding for an activator or repressor of expression of second sequences and (b) regulatory sequences of a characterizing gene corresponding to an endogenous gene or ortholog of an endogenous gene operably linked to said first sequences such that when said transgene is present in the genome of a transgenic animal said first sequences are expressed in said transgenic animal with an expression pattern that is substantially the same as the expression pattern of said endogenous gene in a non-transgenic animal or anatomical region thereof, wherein the characterizing gene is different for each of said vectors.

93. The collection of vectors of claim 92 wherein said second sequences are contained within said transgene.

94. The collection of vectors of claim 92 wherein said second sequences are not contained within said transgene.

95. A method of making a collection of vectors for making transgenic animals said collection comprising two or more of said vectors, said method comprising

- (a) constructing a vector comprising a transgene, said transgene comprising (a) first sequences coding for a selectable or detectable marker protein and (b) regulatory sequences of a characterizing gene corresponding to an endogenous gene or ortholog of an endogenous gene operably linked to said first sequences such that when said transgene is present in the genome of a transgenic animal said first sequences are expressed in said transgenic animal with an expression pattern that is substantially the same as the expression pattern of said endogenous gene in a non-transgenic animal or anatomical region thereof, and
- (b) repeating step (a) one or more times wherein each time step (a) is repeated a different characterizing gene is used;

thereby generating a collection of vectors for making transgenic animals.

96. The method of claim 95 in which said first sequences are introduced into said vector by homologous recombination.

97. The method of claim 96 which is carried out in *E. coli* cells.

98. The method of claim 95 wherein said vectors are BACs.

99. The method of claim 95 wherein said collection comprises ten or more vectors.

100. The method of claim 95 wherein said collection comprises fifty or more vectors.

101. The method of claim 95 wherein said transgene further comprises a coding sequence of said characterizing gene.

102. The method of claim 101 wherein said first sequences are inserted or replace sequences 5' of said coding sequence of said characterizing gene.

103. The method of claim 95 wherein said first sequences are operably linked to an IRES sequence that is not operably linked to a coding sequence of said characterizing gene.

104. The method of claim 101 wherein said first sequences are fused in frame to the ATG start codon of said coding sequence of said characterizing gene.

105. The method of claim 95 wherein said characterizing gene is not functionally expressed from said transgene.

106. The method of claim 95 wherein said first sequences encode a detectable enzyme.

107. The method of claim 106 wherein said detectable enzyme is  $\beta$ -lactamase.

108. The method of claim 95 wherein said first sequences encode a fluorescent protein.

109. The method of claim 108 wherein fluorescent protein is a GFP.

110. The method of claim 95 wherein each said endogenous gene is expressed in the same tissue.

111. The method of claim 95 wherein each said endogenous gene is specifically expressed in a subset of neurons.

112. The method of claim 95 wherein each said endogenous gene is endogenously expressed in neuronal cells.

113. The method of claim 95 wherein each of said endogenous genes endogenously expresses a protein product that is a part of an adrenergic or noradrenergic neurotransmitter pathway, a cholinergic neurotransmitter pathway, a dopaminergic neurotransmitter pathway, a GABAergic neurotransmitter pathway, a glutaminergic

neurotransmitter pathway, a glycinergic neurotransmitter pathway, a histaminergic neurotransmitter pathway, a neuropeptidergic neurotransmitter pathway, a serotonergic neurotransmitter pathway, or the sonic hedgehog signaling pathway, is a nucleotide receptor, an ion channel, a marker of undifferentiated or not fully differentiated nerve cells, a calcium binding protein, or a neurotrophic factor receptor.

114. The method of claim 95 wherein all of said endogenous genes are functionally related.

115. The method of claim 95 wherein each of said endogenous genes are implicated in the same physiological or disease state.

116. The method of claim 115 wherein the physiological or disease state is a neurological or psychiatric disease.

117. The method of claim 116 wherein the neurological or psychiatric disease is schizophrenia, schizotypal personality disorder, psychosis, a schizoaffective disorder manic type disorder, a bipolar affective disorder, a bipolar affective (mood) disorder with hypomania and major depression (BP-II), a unipolar affective disorder, unipolar major depressive disorder, dysthymic disorder, an obsessive-compulsive disorder, a phobia, a panic disorder, a generalized anxiety disorder, a somatization disorder, hypochondriasis, or an attention deficit disorder.

118. The method of claim 95 wherein each of said endogenous genes is implicated in the same physiological or behavioral response.

119. The method of claim 118 wherein said physiological or behavioral response is pain, sleeping, feeding, fasting, sexual behavior or aggression.

120. The method of claim 95 wherein each of said endogenous genes is expressed in neuronal cells involved in regulation of feeding behavior.

121. The method of claim 95 wherein each of said endogenous genes is expressed in a different tissue.

122. The method of claim 95 wherein each of said endogenous genes is implicated in a different physiological or disease state.

123. The method of claim 95 wherein each of said endogenous genes is implicated in the a different physiological or behavioral response.

124 (amended). A transgenic animal comprising a transgene, said transgene comprising (a) first sequences coding for a selectable or detectable marker protein; and (b) regulatory sequences of a characterizing gene corresponding to an endogenous gene or ortholog of an endogenous gene operably linked to said first sequences such that said first sequences are expressed in said transgenic animal with an expression pattern that is substantially the same as the expression pattern of said endogenous gene in a non-transgenic animal or anatomical region thereof, wherein said transgene is present in the genome at a site other than where the endogenous gene is located, said characterizing gene being ADRB1, ADRB2, ADRB3, ADRA1A, ADRA1B, ADRA1C, ADRA1D, ADRA2A, ADRA2B, ADRA2C, SLC6A2, Norepinephrine transporter, CHRM1 (Muscarinic Ach M1) receptor, CHRM2 (Muscarinic Ach M2) receptor, CHRM3 (Muscarinic Ach M3) receptor, CHRM4 (Muscarinic Ach M4) receptor, CHRM5 (Muscarinic Ach M5) receptor, CHRNA1 (nicotinic alpha1) receptor, CHRNA2 (nicotinic alpha2) receptor, CHRNA3 (nicotinic alpha3) receptor, CHRNA4 (nicotinic alpha4) receptor, CHRNA5 (nicotinic alpha5) receptor, CHRNA7 (nicotinic alpha7) receptor, CHRNB1 (nicotinic Beta 1) receptor, CHRNB2 (nicotinic Beta 2) receptor, CHRNB3 ( nicotinic Beta 3) receptor, CHRNB4 (nicotinic Beta 4) receptor, CHRNG nicotinic gamma immature muscle receptor, CHRNE nicotinic epsilon receptor, CHRND nicotinic delta receptor, tyrosine hydroxylase, dopamine transporter, dopamine receptor 1, dopamine receptor 2, dopamine receptor 3, dopamine receptor 4, dopamine receptor 5, dbh, dopamine beta hydroxylase, GABA receptor A2, GABA receptor A3, GABA receptor A4, GABA receptor A5, GABA receptor A6, GABA receptor B1, GABA receptor B2, GABA receptor B3, GABA-A receptor (gamma 1 subunit), GABA-A receptor (gamma 2 subunit), GABA-A receptor (gamma 3 subunit), GABA-A receptor (delta subunit), GABA-A receptor (epsilon subunit), GABA-A receptor (pi

subunit), GABA receptor theta, GABA receptor rho 1, GluR1, GluR2, GluR3, GluR4, GluR5, GluR6, GluR7, GRIK4 (KA1), GRIK5 (KA2), NMDA receptor 1, NMDA receptor 2A, NMDA receptor 2B, NMDA receptor 2C, NMDA receptor 2D, mGluR1a, mGluR2, mGluR3, mGluR4, mGluR5, mGluR6, mGluR7, mGluR8, glut ionotropic delta, glutamate/aspartate transporter II, glutamate transporter GLT1, glutamate transporter SLC1A2, glial high affinity glutamate transporter, neuronal/epithelial high affinity glutamate transporter, glial high affinity glutamate transporter, high affinity aspartate/glutamate transporter, Glycine receptors alpha 1, Glycine receptors alpha 2, Glycine receptors alpha 3, Glycine receptors alpha 4, glycine receptor beta, histamine H1-receptor 1, Histamine H2-receptor 2, Histamine H3-receptor 3, orexin OX-A, Orexin receptor OX1R, Orexin receptor OX2R, Leptin receptor long form, melanin concentrating hormone, melanocortin 3 receptor, melanocortin 4 receptor, melanocortin 5 receptor, corticotropin releasing hormone, CRH/CRF receptor 1, CRH/CRF receptor 2, CRF binding protein, Urocortin, Pro-opiomelanocortin, cocaine and amphetamine regulated transcript, Neuropeptide Y, Neuropeptide Y1 receptor, Neuropeptide Y2 receptor, Npy4R Neuropeptide Y4 receptor, Npy5R Neuropeptide Y5 receptor, Npy6r Neuropeptide Y receptor, cholecystokinin, CCKAR cholecystokinin receptor, CCKBR cholecystokinin receptor, agouti related peptide, Galanin, Galanin like peptide, galanin receptor1, galanin receptor2, galanin receptor3, prepro-urotensin II, Urotensin receptor, somatostatin, somatostatin receptor sst1, somatostatin receptor sst2, somatostatin receptor sst3, somatostatin receptor sst4, somatostatin receptor sst5, G protein-coupled receptor 7, opioid-somatostatin-like receptor, G protein-coupled receptor 8 opioid-somatostatin-like receptor, pre Pro Enkephalin, Pre pro Dynorphin,  $\mu$  opiate receptor, kappa opiate receptor, delta opiate receptor, ORL1 opioid receptor-like receptor, Vanilloid receptor subtype 1, protein 1 VRL1, vanilloid receptor-like protein 1, vanilloid receptor-related osmotically activated channel, cannaboid receptors CB1, endothelin 1 ET-1 growth hormone releasing hormone, growth hormone releasing hormone receptor, nociceptin orphanin FQ/nocistatin, neuropeptide FF precursor, G-protein coupled receptor NPGPR, gastrin releasing peptide, preprogastrin-releasing peptide, gastrin releasing peptide receptor BB2, neuromedin B, neuromedin B receptor BB1, bombesin like receptor subtype-3, uterine bombesin receptor, GCG PROglucagon, glucagon receptor, GLP1 receptor, GLP2 receptor, vasoactive intestinal peptide, secretin, pancreatic polypeptide receptor 1, pre-pro-Oxytocin, oxytocin receptor, Preprovasopressin, vasopressin receptor 1a, vasopressin receptor 1b, vasopressin

receptor 2, Neurotensin tridecapeptide plus neuromedin N, Neurotensin receptor NT1, Neurotensin receptor NT2, sortilin 1 neurotensin receptor 3, Bradykinin receptor 1, Bradykinin receptor B2, gonadotrophin releasing hormone, gonadotrophin releasing hormone, gonadotrophin releasing hormone receptor, calcitonin-related polypeptide, beta, calcitonin/calcitonin-related polypeptide alpha, calcitonin receptor, neurokinin A, neurokinin B, neurokinin a (subK) receptor, tachykinin receptor NK2 (Sub P and K), tachykinin receptor NK3 (Sub P and K) neuromedin K, PACAP, atrial natriuretic peptide (ANP) precursor, atrial natriuretic peptide (BNP) precursor, natriuretic peptide receptor 1, natriuretic peptide receptor 2, natriuretic peptide receptor 3, VIP receptor 1, PACAP receptor, serotonin receptor 1A, serotonin receptor 2A, serotonin receptor 3, serotonin receptor 1B, serotonin receptor 1D, serotonin receptor 1E, serotonin receptor 2B, serotonin receptor 2C, serotonin receptor 4, serotonin receptor 5A, serotonin receptor 5B, serotonin receptor 6, serotonin receptor 7, serotonin transporter, tryptophan hydroxylase, purinergic receptor P2X ligand-gated ion channel, purinergic receptor P2X ligand-gated ion channel 3, purinergic receptor P2X ligand-gated ion channel 4, purinergic receptor P2X ligand-gated ion channel 5, purinergic receptor P2X-like 1 orphan receptor, purinergic receptor P2X ligand-gated ion channel 7, purinergic receptor P2Y G-protein coupled 1, purinergic receptor P2Y G-protein coupled 2, pyrimidinergic receptor P2Y G-protein coupled 4, pyrimidinergic receptor P2Y G-protein coupled 6, purinergic receptor P2Y G-protein coupled 11, voltage gated sodium channel type I alpha, sodium channel voltage-gated type I beta, sodium channel voltage-gated type II beta, sodium channel voltage-gated type V alpha, sodium channel voltage-gated type II alpha 1, sodium channel voltage-gated type II alpha 2, sodium channel voltage-gated type III alpha, sodium channel voltage-gated type IV alpha, sodium channel voltage-gated type VII or VI, sodium channel voltage-gated type VIII, sodium channel voltage-gated type IX alpha, sodium channel voltage-gated type X, sodium channel voltage-gated type XI alpha, sodium channel voltage-gated type XII alpha, sodium channel nonvoltage-gated 1 alpha, sodium channel voltage-gated type IV beta, sodium channel nonvoltage-gated 1 beta, sodium channel nonvoltage-gated 1 delta, sodium channel nonvoltage-gated 1 gamma, chloride channel 1 skeletal muscle, chloride channel 2, chloride channel 3, chloride channel 4, chloride channel 5, chloride channel 6, chloride channel 7, chloride intracellular channel 1, chloride intracellular channel 2, chloride intracellular channel 3, chloride intracellular channel 5, chloride channel Kb, chloride channel Ka, chloride channel, calcium activated family member 1, chloride channel calcium

activated family member 2, chloride channel calcium activated family member 3, chloride channel calcium activated family member 4, potassium voltage-gated channel shaker-related subfamily member 1, potassium voltage-gated channel shaker-related subfamily member 2, potassium voltage-gated channel shaker-related subfamily member 3, potassium voltage-gated channel shaker-related subfamily member 4, potassium voltage-gated channel shaker-related subfamily member 4-like, potassium voltage-gated channel shaker-related subfamily member 5, potassium voltage-gated channel shaker-related subfamily member 6, potassium voltage-gated channel shaker-related subfamily member 7, potassium voltage-gated channel shaker-related subfamily member 10, potassium voltage-gated channel Shab-related subfamily member 1, potassium voltage-gated channel Shab-related subfamily member 2, potassium voltage-gated channel Shaw-related subfamily member 1, potassium voltage-gated channel Shaw-related subfamily member 2, potassium voltage-gated channel Shaw-related subfamily member 3, potassium voltage-gated channel Shaw-related subfamily member 4, potassium voltage-gated channel Shal-related family member 1, potassium voltage-gated channel Shal-related subfamily member 2, potassium voltage-gated channel Shal-related subfamily member 3, potassium voltage-gated channel Isk-related family member 1, potassium voltage-gated channel Isk-related family member 1-like, potassium voltage-gated channel Isk-related family member 2, potassium voltage-gated channel Isk-related family member 3, potassium voltage-gated channel Isk-related family member 4, potassium voltage-gated channel subfamily F member 1, potassium voltage-gated channel subfamily G member 1, potassium voltage-gated channel subfamily G member 2, potassium voltage-gated channel subfamily H (eag-related) member 1, potassium voltage-gated channel subfamily H (eag-related) member 2, potassium voltage-gated channel subfamily H (eag-related) member 3, potassium voltage-gated channel subfamily H (eag-related) member 4, potassium voltage-gated channel subfamily H (eag-related) member 5, potassium inwardly-rectifying channel subfamily J member 1, potassium inwardly-rectifying channel subfamily J member 2, potassium inwardly-rectifying channel subfamily J member 3, potassium inwardly-rectifying channel subfamily J member 4, potassium inwardly-rectifying channel subfamily J member 5, potassium inwardly-rectifying channel subfamily J member 6, potassium inwardly-rectifying channel subfamily J member 8, potassium inwardly-rectifying channel subfamily J member 9, potassium inwardly-rectifying channel subfamily J member 10, potassium inwardly-rectifying channel subfamily J member 11, potassium inwardly-rectifying channel subfamily J member 12,

potassium inwardly-rectifying channel subfamily J member 13, potassium inwardly-rectifying channel subfamily J member 14, potassium inwardly-rectifying channel subfamily J member 15, potassium inwardly-rectifying channel subfamily J member 1, potassium channel, subfamily K member 1, potassium channel subfamily K member 2, potassium channel subfamily K member 3, potassium inwardly-rectifying channel subfamily K member 4, potassium channel subfamily K member 5, potassium channel subfamily K member 6, potassium channel subfamily K member 7, potassium channel subfamily K member 8, potassium channel subfamily K member 9, potassium channel subfamily K member 10, potassium intermediate/small conductance calcium-activated channel subfamily N member 1, potassium intermediate/small conductance calcium-activated channel subfamily member 2, potassium intermediate/small conductance calcium-activated channel subfamily N member 4, potassium voltage-gated channel KQT-like subfamily member 1, potassium voltage-gated channel KQT-like subfamily member 2, potassium voltage-gated channel KQT-like subfamily member 3, potassium voltage-gated channel KQT-like subfamily member 4, potassium voltage-gated channel KQT-like subfamily member 5, potassium voltage-gated channel delayed-rectifier, subfamily S member 1, potassium voltage-gated channel, delayed-rectifier, subfamily S member 2, potassium voltage-gated channel delayed-rectifier subfamily S member 3, potassium voltage-gated channel shaker-related subfamily beta member 1, potassium voltage-gated channel shaker-related subfamily beta member 2, potassium voltage-gated channel shaker-related subfamily beta member 3, potassium inwardly-rectifying channel subfamily J inhibitor 1, potassium large conductance calcium-activated channel subfamily M alpha member 1, potassium large conductance calcium-activated channel subfamily M alpha member 3, potassium large conductance calcium-activated channel subfamily M beta member 1, potassium large conductance calcium-activated channel subfamily M beta member 2, potassium large conductance calcium-activated channel subfamily M beta member 3-like, potassium large conductance calcium-activated channel, potassium large conductance calcium-activated channel sub M beta 4, hyperpolarization activated cyclic nucleotide-gated potassium channel 1, calcium channel voltage-dependent L type alpha 1S subunit, calcium channel voltage-dependent L type alpha 1C subunit, calcium channel voltage-dependent L type alpha 1D subunit, calcium channel voltage-dependent L type alpha 1F subunit, type calcium channel voltage-dependent P/Q type alpha 1A subunit, calcium channel voltage-dependent L type alpha 1B subunit, calcium channel voltage-

dependent alpha 1E subunit, calcium channel voltage-dependent alpha 1G subunit, calcium channel, voltage-dependent alpha 1H subunit, calcium channel voltage-dependent alpha 1I subunit, NES (nestin), scip, sonic hedgehog, Smoothed Shh receptor, Patched Shh binding protein, calbindin d28 K, calretinin, parvalbumin, Trk B, GFR alpha 1, GFRalpha 2, GFRalpha 3, Neurotrophin receptor, Neurotrophin receptor, or Neurotrophic factor receptor.

125. The transgenic animal of claim 124 wherein said transgene further comprises a coding sequence of said characterizing gene.

126. The transgenic animal of claim 125 wherein said first sequences are inserted or replace sequences 5' of said coding sequence of said characterizing gene.

127. The transgenic animal of claim 124 wherein said first sequences are operably linked to an IRES sequence that is not operably linked to a coding sequence of said characterizing gene.

128. The transgenic animal of claim 125 wherein said first sequences are fused in frame to the ATG start codon of said coding sequence of said characterizing gene.

129. The transgenic animal of claim 124 wherein said characterizing gene is not functionally expressed from said transgene.

130. The transgenic animal of claim 124 wherein said first sequences encode a detectable enzyme.

131. The transgenic animal of claim 130 wherein said detectable enzyme is  $\beta$ -lactamase.

132. The transgenic animal of claim 124 wherein said first sequences encode a fluorescent protein.

133. The transgenic animal of claim 133 wherein fluorescent protein is a green fluorescent protein (GFP).

134 (amended). A transgenic animal comprising two or more transgenes, each said transgene comprising (a) first sequences coding for a selectable or detectable marker protein; and (b) regulatory sequences of a characterizing gene corresponding to an endogenous gene or ortholog of an endogenous gene operably linked to said first sequences such that said first sequences are expressed in said transgenic animal with an expression pattern that is substantially the same as the expression pattern of said endogenous gene in a non-transgenic animal or anatomical region thereof, wherein the characterizing gene is different for each said transgenes, and wherein each said transgene is present in the genome at a site other than where the endogenous gene is located.

135. The transgenic animal of claim 134 comprising 5 or more of said transgenes.

136. A method of isolating a collection of pure populations of cells wherein said collection comprises at least two different populations of cells, said method comprising isolating from two or more transgenic animals from the collection of transgenic animals of claim 1 or claim 28 the cells expressing said selectable or detectable marker from cells not expressing said selectable or detectable marker.

137. The method of claim 136 wherein said transgenic animals are transgenic mice.

138. The method of claim 136 wherein said collection comprises ten or more populations of cells.

139. The method of claim 136 wherein said collection comprises fifty or more populations of cells.

140. The method of claim 136 wherein said first sequences encode a detectable enzyme.

141. The method of claim 140 wherein said detectable enzyme is  $\beta$ -lactamase.
142. The method of claim 136 wherein said first sequences encode a fluorescent protein.
143. The method of claim 142 wherein fluorescent protein is a GFP.
144. The method of claim 142 wherein said isolating is by fluorescence activated cell sorting (FACS).
145. The method of claim 136 which further comprises culturing said isolated populations of cells.
- 146 (amended). A collection of pure populations of cells isolated from the transgenic animals of the collection of lines of transgenic animals of claim 1 or 28, wherein said cells express said detectable or selectable marker and each of said pure populations is isolated from a transgenic animal having a different characterizing gene.
147. A method of screening a candidate molecule for an effect on one or more cell types, said method comprising
- (a) contacting said molecule to cells from each pure population of cells in the collection of claim 146; and
  - (b) detecting a change in said cells in response to said contacting.
148. The method of claim 147 wherein said change is measured by electrophysiology.
149. The method of claim 147 wherein said change is a change in gene expression.
150. The method of claim 149 wherein said change in gene expression is detected by hybridization of mRNA isolated from said cells to a microarray.

151. The method of claim 147 wherein said change is a change in cell morphology, cell proliferation, contact inhibition, or DNA replication.

152. The method of claim 147 wherein each pure population of cells in said collection was isolated from the transgenic animal which had been bred to a disease model of the same species or in which a disease state had been induced.

153 (amended). A method of screening a candidate molecule for an effect on one or more cell types, said method comprising

- (a) administering said candidate molecule to a transgenic animal from each line of transgenic animals of the collection of transgenic animals of claim 1;
- (b) isolating a pure population of cells from each of said transgenic animals that express said first sequences from the cells that do not express said first sequences; and
- (c) detecting a change in said pure populations of cells from said transgenic animals administered said candidate molecule in comparison to corresponding pure populations of cells from transgenic animals from said lines of transgenic animals not administered said candidate molecule.

154. The method of claim 153 wherein said change is measured by electrophysiology.

155. The method of claim 153 wherein said change is a change in gene expression.

156. The method of claim 155 wherein said change in gene expression is detected by hybridization of mRNA isolated from said cells to a microarray.

157. The method of claim 153 wherein said change is a change in cell morphology, cell proliferation, contact inhibition, or DNA replication.

158. The method of claim 153 wherein each said transgenic animal had been bred to a disease model of the same species or in which a disease state had been induced.